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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,251	02/14/2006	Sarah S. Bacus	PR60446USw	9708

23347 7590 05/23/2008

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
05/23/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/568,251	BACUS ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 19-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-18* is/are rejected.

7)☒ Claim(s) *16-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction

The response filed on 3/6/08 to the restriction requirement of 2/28/08 has been received. Applicant has elected Group II, claims 10-18 for examination. Because Applicant did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-38 are pending.

Claims 1-9 and 19-38 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 10-18 are currently under consideration.

Claim Objections

Claims 16-17 are objected to because of apparent typographical errors. Claims 16-17 recite "…to claim 10where said…". There appears to be a space missing between "10" and "where". It is suspected Applicant intended claims 16-17 to recite: "…to claim 10_where said…". Proper correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al (Oncogene, September 2002, 21:6255-6263) in view of Meier et al (JBC, November 1997, 272(48):30491-30497).

Claim 10 is drawn to a method to assess whether a human subject in need of treatment with a therapeutic compound for an EGFR-expression or erbB2-expressing solid tumor is likely to exhibit a favorable clinical response to treatment with a dual EGFR/erbB2 tyrosine kinase inhibitor compound, comprising: (a) detecting the pre-treatment relative localization of pAKT in cells of said tumor, (b) administering a therapeutically effective amount of a dual EGFR/erbB2 tyrosine kinase inhibitor, and (c) determining the relative localization of pAKT in cells of said tumor after an initial period of treatment with said therapeutic agent, where a shift in the relative pAKT localization from the nucleus to the cytoplasm indicates said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a

subject with no change in relative pAKT localization. Claim 11 is drawn to a method according to claim 10 where said initial period of treatment is the time required to achieve a steady-state plasma concentration of said therapeutic compound. Claim 12 is drawn to a method according to claim 10 wherein p-AKT levels are assessed by immunohistochemical methods. Claim 13 is drawn to the method of claim 10 where said tumor over-expresses EGFR or erbB2. Claim 14 is drawn to a method according to claim 10 where said solid tumor is an epithelial tumor. Claim 15 is drawn to a method according to claim 10 where said tumor is selected from breast, ovarian, colon, head and neck, bladder, renal cell and lung tumors. Claim 16 is drawn to a method according to claim 10 where said therapeutic agent is GW572016. Claim 17 is drawn to a method according to claim 10 where said therapeutic agent is GW572016 and said initial treatment period is from about 14 to about 28 days

Xia et al teaches a method to assess whether a human subject in need of treatment with a therapeutic compound for an EGFR-expression or erbB2-expressing solid tumor is likely to exhibit a favorable clinical response to treatment with the dual EGFR/erbB2 tyrosine kinase inhibitor compound GW572016 comprising detecting evidence of activated EGFR or erbB2 (left column of page 6261, in particular). Xia et al further teaches that pErk and pAKT are indicative of activated ERGFR and erbB2 (Figure 2 and pages 6256-6257, in particular). Xia et al further teaches methods of detecting pre-treatment levels of pErk and pAKT in tumors, administering GW572016, and detecting levels of pErk and pAKT in cells of said tumor after an initial period of treatment with GW572016, where a decrease in levels of pErk and pAKT indicates that

GW572016 is giving rise to a favorable clinical response by inhibiting mitogenic signals transduced through growth factor receptors (Figure 7 and pages 6259-6260, in particular), as compared to a subject exhibiting no change in relative pAKT levels. Xia et al further teaches a method where said initial period of treatment is a time that would achieve a steady-state plasma concentration of said therapeutic compound (page 6262, in particular). Xia et al further teaches a method wherein p-AKT levels are assessed by immunohistochemical methods (see Figure 7, in particular). Xia et al further teaches a method wherein said solid tumor is an epithelial tumor selected from breast, ovarian, colon, head and neck, bladder, renal cell and lung tumors (see page 6262, in particular). Xia et al further teaches a method wherein said initial treatment period is from "about" 14 to "about" 28 days (page 6262 and Figure 7, in particular).

Xia et al does not specifically teach methods wherein activated EGFR or erB2 are detected by a shift in relative pAKT localization from the nucleus to the cytoplasm. However, these deficiencies are made up in the teachings of Meier et al.

Meier et al teaches AKT is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 7, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use levels of pAKT in the nucleus as a measure of activated EGFR or erbB2 when performing the method of Xia et al, where a shift in a subject's relative pAKT localization from the nucleus to the cytoplasm indicates GW572016 inhibits EGFR or erbB2 activation and that said subject is more likely to exhibit a favorable clinical response to GW572016 than a subject where activated pAKT is localized in the

nucleus, because Meier et al teaches AKT is phosphorylated and shifts from the cytoplasm to the nucleus upon activation (see abstract and Figure 7, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using levels of pAKT in the nucleus as a measure of activated EGFR or erbB2 when performing the method of Xia et al, where a shift in relative pAKT localization from the nucleus to the cytoplasm in a subject indicates GW572016 inhibits EGFR or erbB2 activation and that said subject is more likely to exhibit a favorable clinical response to GW572016 than a subject where activated pAKT is localized in the nucleus, because Meier et al teaches AKT is phosphorylated and shifts from the cytoplasm to the nucleus upon activation (see abstract and Figure 7, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al (Oncogene, September 2002, 21:6255-6263) in view of Meier et al (JBC, November 1997, 272(48):30491-30497) as applied to claims 1-17 above, and further in view of Zheng et al (JBC, August 1994, 269(31): 19947-19952).

The teaching of claims 1-17 by the combined teachings of Xia et al and Meier et al are discussed above. The combined teachings of Xia et al and Meier et al do not specifically teach a method wherein activated EGFR or erbB2 is detected by a shift in

relative pErk localization. However, this deficiency is made up in the teachings of Zheng et al.

Zheng et al teaches Erk is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 6, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to determine the relative localization of pErk in cells of said tumor pre-treatment and after the initial period of treatment as a measure of activated EGFR or erbB2 when performing the combined method of Xia et al and Meier et al because Xia et al teaches a decrease in Erk activation indicates that GW572016 is giving rise to a favorable clinical response by inhibiting mitogenic signals transduced through growth factor receptors (Figure 7 and pages 6259-6260, in particular) and Zheng et al teaches Erk is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 6, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for determining the relative localization of pErk in cells of said tumor pre-treatment and after the initial period of treatment as a measure of activated EGFR or erbB2 when performing the combined method of Xia et al and Meier et al because Zheng et al teaches method of determining the relative localization of pErk in cells (Figure 6, in particular**).** Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rusnak et al (Molecular Cancer Therapeutics, December 2001, 1:85-94) in view of Meier et al (JBC, November 1997, 272(48):30491-30497).

Note that Rusnak et al refers to “GW572016” as “GW2016” (compare the description of "GW2016” on page 86 of Rusnak et al with the disclosed definition of "GW572016" at lines 26-30 on page 18 of the instant specification).

Rusnak et al teaches a method to assess whether a subject in need of treatment with a therapeutic compound for an EGFR-expression or erbB2-expressing solid tumor exhibits a favorable clinical response to treatment with the dual EGFR/erbB2 tyrosine kinase inhibitor compound GW572016 comprising *detecting inhibition of tumor growth* upon treatment with GW572016 (see pages 90-93, in particular). Rusnak et al further teaches that GW572016 functions as an inhibitor of EGFR and ErbB2 and that activation of AKT is indicative of activated EGFR or erbB2 (Figure 6 and page 90, in particular). Rusnak et al further teaches methods of detecting pre-treatment levels of pAKT in HN7 and BT474 cell lines, administering GW572016, and detecting levels of pAKT in cells of said cell line after an initial period of treatment with GW572016, where a decrease in levels of pAKT indicate that GW572016 is giving rise to a favorable response by inhibiting mitogenic signals transduced through growth factor receptors (Figure 6 and pages 90-93, in particular), as compared to cells exhibiting no change in relative pAKT levels. Rusnak et al further teaches a method where subjects are treated with GW572016 for a period of that would achieve a steady-state plasma concentration of said therapeutic compound (Figure 7, in particular). Rusnak et al further teaches a

method wherein p-AKT levels are assessed by immunohistochemical methods (see Figure 6, in particular). Rusnak et al further teaches a method wherein said solid tumor is an epithelial tumor selected from breast, ovarian, colon, head and neck, bladder, renal cell and lung tumors (see Figure 7 and page 86, in particular). Rusnak et al further teaches a method wherein subjects are treated from "about" 14 to "about" 28 days (Figure 7, in particular). Rusnak et al further teaches GW572016 inhibits ERK activity (see Table 1, in particular).

Rusnak et al does not specifically teach methods of assessing whether a human subject in need of treatment with a therapeutic compound for an EGFR-expression or erbB2-expressing solid tumor is likely to exhibit a favorable clinical response to treatment with a dual EGFR/erbB2 tyrosine kinase inhibitor compound, comprising: (a) detecting the pre-treatment relative localization of pAKT in cells of said tumor, (b) administering a therapeutically effective amount of a dual EGFR/erbB2 tyrosine kinase inhibitor, and (c) determining the relative localization of pAKT in cells of said tumor after an initial period of treatment with said therapeutic agent, where a shift in the relative pAKT localization from the nucleus to the cytoplasm indicates said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a subject with no change in relative pAKT localization. Further, Rusnak et al does not specifically teach said method where said initial period of treatment is the time required to achieve a steady-state plasma concentration of GW572016, where p-AKT levels are assessed by immunohistochemical methods, where said tumor over-expresses EGFR or erbB2, where said solid tumor is an epithelial tumor selected from

breast, ovarian, colon, head and neck, bladder, renal cell and lung tumors, and wherein said therapeutic agent is GW572016 and wherein said initial treatment period is from about 14 days to about 28 days. However, these deficiencies are rendered obvious and/or made up in the teachings of Meier et al.

Meier et al teaches AKT is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 7, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform a method using levels of pAKT in the nucleus after an initial treatment for a period of time required to achieve steady-state plasma concentrations with GW572016, as compared to levels of pAKT in the nucleus prior to said initial treatment, as a measure of activated EGFR or erbB2 when assessing whether a human subject in need of treatment with a therapeutic compound for an EGFR-expression or erbB2-expressing solid tumor is likely to exhibit a favorable clinical response to treatment with the dual EGFR/erbB2 tyrosine kinase inhibitor compound GW572016 comprising detecting evidence of activated EGFR or erbB2, where a shift in relative pAKT localization from the nucleus to the cytoplasm (less pAKT in the nucleus) indicates GW572016 inhibits EGFR or erbB2 activation and that said subject is more likely to exhibit a favorable clinical response to GW572016 as compared to a subject with no change in relative pAKT localization, because Rusnak et al teaches GW572016 is a EGFR/erbB2 tyrosine kinase inhibitor compound that promotes therapeutic effects by inhibiting EGFR and erbB2 signaling through pathways involving AKT activation (pages 90-93 and Figure 6, in particular), Meier et al teaches AKT is phosphorylated

and shifts from the cytoplasm to the nucleus upon activation (see abstract and Figure 7, in particular). Further, one would have been motivated to perform said method where p-AKT levels are assessed by immunohistochemical methods because Rusnak et al and Meier et al teach methods of detecting p-AKT by immunohistochemical methods (Figure 6 of Rusnak and Figure 7 of Meier et al, in particular). Further, one would have been motivated to perform said method where said subject is human and said tumor over-expresses EGFR or erbB2 and is an epithelial tumor selected from breast, ovarian, colon, head and neck, bladder, renal cell and lung tumors because Rusnak et al teaches GW572016 treats human tumors overexpressing EGFR or erbB2 and are epithelial tumors selected from breast, ovarian, colon, head and neck, bladder, renal cell and lung tumors (Figure 7, in particular). Further, one would have been motivated to perform said method where said initial treatment period is from about 14 days to about 28 days because Rusnak et al teaches detecting effects of GW572016 after about 14 days to about 28 days (see Figure 7, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing said method, because Meier et al teaches AKT is phosphorylated and shifts from the cytoplasm to the nucleus upon activation (see abstract and Figure 7, in particular). Further, one would have been motivated to performs said method because Rusnak et al teaches GW572016 is a EGFR/erbB2 tyrosine kinase inhibitor compound that promotes therapeutic effects by inhibiting EGFR and erbB2 signaling through pathways involving AKT activation (pages 90-93 and Figure 6, in particular) and Meier et al teaches AKT is phosphorylated and shifts from the cytoplasm to the nucleus upon

activation (see abstract and Figure 7, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rusnak et al (Molecular Cancer Therapeutics, December 2001, 1:85-94) in view of Meier et al (JBC, November 1997, 272(48):30491-30497) as applied to claims 1-17 above, and further in view of Spencer et al (J Cell Biol, January 2000, 148(2):385-97) and Zheng et al (JBC, August 1994, 269(31): 19947-19952).

Teaching of claims 1-17 by the combined teachings of Rusnak et al and Meier et al is discussed above. The combined teachings of Rusnak et al and Meier et al do not specifically teach a method wherein activated EGFR or erbB2 is detected by a shift in relative pErk localization. However, this deficiency is made up in the teachings of Spencer et al and Zheng et al.

Spencer et al teaches mitogenic activation of ErbB2 contributes to the aggressive behavior of breast cancer through Erk activation (see abstract, in particular).

Zheng et al teaches Erk is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 6, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to detect a therapeutic response from the ErbB2 inhibitor GW572016 in the combined method of Rusnak et al and Meier et by a shift in relative pErk localization because Rusnak et al teaches GW572016 inhibits ErbB2 (see abstract, in particular),

Spencer et al teaches mitogenic activation of ErbB2 contributes to the aggressive behavior of breast cancer through Erk activation (see abstract, in particular), and Zheng et al teaches Erk is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 6, in particular). Therefore, a shift in relative pErk localization (with less pErk in the nucleus) would be indicative of a therapeutic response. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for detecting a therapeutic response to the ErbB2 inhibitor GW572016 in the combined method of Rusnak et al and Meier et by a shift in relative pErk localization because Rusnak et al teaches GW572016 inhibits ErbB2 (see abstract, in particular), Spencer et al teaches mitogenic activation of ErbB2 contributes to the aggressive behavior of breast cancer through Erk activation (see abstract, in particular), and Zheng et al teaches Erk is phosphorylated and translocates from the cytoplasm to the nucleus upon mitogenic activation (see abstract and Figure 6, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642